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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/785,793	02/16/2001	Bertrand Seraphin	70436	5538

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EXAMINER	
HINES, JANA A	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 07/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/785,793	SERAPHIN ET AL.	
	Examiner	Art Unit	
	Ja-Na Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 5, 2005 has been entered.

2. Claims 1-12 are under consideration in this office action.

Withdrawal of Rejections

3. The rejection of claims 1-11 under 35 U.S.C. 112, second paragraph, is withdrawn in view of Applicants" amendments and arguments.

Response to Arguments

4. Applicant's arguments filed May 5, 2005 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. The scope of enablement rejection of claims 1-12 under 35 U.S.C. 112, first paragraph, is maintained for reasons already of record. The rejection was on the grounds that the claims are not enabled for a method for purifying biomolecules and/or protein complexes, the method comprising: (a) providing an expression environment containing one or more heterologous nucleic acids encoding one or more subunits of a biomolecule complex; (b) maintaining the expression environment under conditions that facilitate expression of the one or more subunits in a native form as fusion proteins with subunits being fused to at least two different affinity tags, wherein one of the affinity tags consists of one or more IgG binding domains of Staphylococcus protein A; and (c) purifying the one or more subunits by a combinations of at least two different affinity purification steps each comprising binding the one or more subunits via one affinity tag to a support material capable of selectively binding one of the affinity tags and separating the one or more subunits from the support material after substances not bound to the support material have been removed to provide a purified biomolecule and/or protein complex.

Applicants' state that the method takes place irrespective of the nucleic acid sequence. However it is unclear how one can be enabled for a method of purifying these one or more heterologous nucleic acids if one does not know what is being purified and if one does not know the maximum number of heterologous sequences encoding a limitless number of subunits. The claim language drawn to heterologous nucleic acids encoding one or more subunits of a biomolecule complex which embraces sequences without disclosing the actual

nucleic acid sequences. Therefore the claims embrace nucleic acids encoding undiscovered subunits and clearly applicant is not enabled for such. Applicants' urge that a skilled person could easily identify a corresponding nucleic acid. However, the claims are not enabled to embrace a limitless number of heterologous nucleic acids which encode random subunits. Therefore without specific information regarding the heterologous nucleic acids, one of skill in the art could not predict which heterologous nucleic acids would result in the desired encoded one or more subunits of a biomolecule complex, thereby requiring undue experimentation, contrary to applicants' assertions. Therefore, one of skill in the art would be required to perform undue experimentation to use the claimed method for purifying biomolecules and/or protein complexes. One skilled in the art could not make and/or use the invention without undue experimentation and the rejection is maintained. Applicants' generalization that no undue experimentation is required is not found persuasive in view of the quantity of experimentation, lack of guidance and working examples and the state of the prior art previously addressed. Therefore the rejection is maintained.

The claims are not enabled for providing a generic expression environment containing any type of heterologous nucleic acids encoding one or more subunits of a biomolecule complex, since this includes unidentified heterologous nucleic acids, contrary to applicants' statement that the invention does not relate to nucleic acid sequences and protein complexes per se. Also, the claims are only enabled when the method also comprises concentrating the

eluted proteins using precipitation techniques; and detecting the concentrated proteins by polyacrylamide gel electrophoreses.

Applicants' merely assert that undue experimentation is not required. However, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims. The instant examples recite that the method comprises providing a vector encoding a fusion of a yeast protein to the Calmodulin Binding Peptide-Tobacco Etch Virus protease NIA – Staphylococcus Protein A (CBP-TEV-Protein A) double tag wherein the fusion protein is one subunit of a protein complex of yeast containing 24 subunits and the plasmid is transformed in to the yeast cell. There are no examples commensurate in scope to the broad claims. The claims are only enabled for complexes from a yeast host. Furthermore, the claims are only enabled for encoding a fusion of a yeast protein to the Calmodulin Binding Peptide-Tobacco Etch Virus protease NIA –Staphylococcus Protein A (CBP-TEV-Protein A) double tag wherein the fusion protein is one subunit of a protein complex of yeast containing 24 subunits and the plasmid is transformed in to the yeast cell.

The teaching within the specification is limited to the specific steps and reagents recited in the instant specification. The specification fails to teach examples of purifying biomolecules and protein complexes, such that without the exact and precise method steps and specific reagents the claimed detection and purification methods could not be achieved. The broad method claims do not require the precise and active steps and reagents thus, one of ordinary skill in the

art would be required to determine the appropriate reagents and conditions required to achieve the claimed method. Therefore, the guidance presented is narrowly tailored to the working examples and not to the broad claims and applicants' argument are not persuasive.

Applicants' broadly state that each individual aspect of the claims would have been routine to one skilled in the art, however it is the examiner's position that without the exact and precise method steps and specific reagents the claimed detection and purification methods could not be achieved. Moreover, Applicants' own disclosure supports that without exact and precise method steps and specific reagents the claimed detection and purification methods could not be achieved.

6. The written description rejection of claims 1-12 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for reasons already of record. The rejection was on the grounds that the specification and claims lack sufficient written description of the generically claimed an expression environment containing one or more heterologous nucleic acids encoding one or more subunits of a biomolecule complex.

Applicants' urge that the one of ordinary skill in the art would clearly understand how to provide an expression environment containing one or more heterologous nucleic acids encoding one or more subunits of a biomolecule complex. However, it is noted that the one or more heterologous nucleic acids are defined by their activity or function, i.e., the ability to encode one or more

subunits of a biomolecule complex and do not describe the one or more heterologous nucleic acids. As previously stated, the encoding distinction is a purely functional distinction and a description of the heterologous nucleic acid by what it does, such as encoding one or more subunits of a biomolecule complex is insufficient. The written description of the one or more heterologous nucleic acids encoding one or more subunits of a biomolecule complex is insufficient when the specification fails to disclose an example of heterologous nucleic acid sequences that can be used in the claimed method.

The specification does not provide evidence that a heterologous nucleic acid, as claimed, functions with the ability to encoded one or more subunits of a biomolecule complex. Applicants' have not provided evidence to the contrary. The instant specification and claims are encompassing currently unknown sequences and claims that these nucleic acid sequences can be used to in the method of detection and purification. Therefore is evident that other heterologous nucleic acids have not yet been identified. Moreover, the instant specification fails to disclose specific heterologous nucleic acid sequences; rather the specification broadly defines the sequences to be any and every nucleic acid sequence without any discretion. In view of the lack of evidence, it is apparent that applicants' were not in possession of all or many heterologous nucleic acid sequences that encode one or more subunits of a biomolecule complex at the time of filing the instant application. The skilled artisan cannot envision the detailed structure of a method for detecting and/or purifying biomolecule and/or protein complexes in the method comprising providing an expression

environment containing one or more heterologous nucleic acids encoding one or more subunits of a biomolecules complex. Thus conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation despite applicants' assertions to the contrary.

Thus, the one or more heterologous nucleic acids described only by their ability to encode fails to meet the written description requirements. Therefore the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph and the rejection is maintained.

New Grounds of Rejection

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-9 and 11-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Darzins et al., (WO 96/40943 published December 19, 1996). It is noted that the Darzins et al., is being reinstated. Applicants' previous arguments to this art are addressed below.

The claims are drawn to a method for purifying biomolecules and/or protein complexes, the method comprising: (a) providing an expression environment containing one or more heterologous nucleic acids encoding one or

more subunits of a biomolecule complex; (b) maintaining the expression environment under conditions that facilitate expression of the one or more subunits in a native form as fusion proteins with subunits being fused to at least two different affinity tags, wherein one of the affinity tags consists of one or more IgG binding domains of Staphylococcus protein A; and (c) purifying the one or more subunits by a combinations of at least two different affinity purification steps each comprising binding the one or more subunits via one affinity tag to a support material capable of selectively binding one of the affinity tags and separating the one or more subunits from the support material after substances not bound to the support material have been removed to provide a purified biomolecule and/or protein complex. The dependant claims are drawn to a specific proteolytic cleavage sites for Tobacco Etch Virus protease NIA; specific affinity purification steps, the use of chemical reagents and detection of the purified complex.

Darzins et al., teach the construction and use of expression vectors comprising a method for expressing proteins whereby the desired protein product is purified (page 8-9, lines 28-2). The methods teach the construction and use of host/vector systems that use heterologous proteins configurations fused to a combination of polyhistidine tags and protein A IgG binding domains of Staphylococcus, Factor Xa or Tobacco Etch Virus (TEV) protease cleavage sites (page 9, lines 10-14). All of which are affinity tags as taught by the instant specification at page 3, lines 4-16. The recombinant proteins can then be purified after cleavage with a specific protease, just as instantly claimed (page 9, lines

16-19). The construction of heterologous fusion proteins, includes small DNA fragments containing the recognition sequences that can be placed between the DNA sequences that encode the amino and carboxy terminal sorting signal whereby this multiple cloning site will facilitate the insertion of heterologous protein coding sequences and upon expression will generate in-frame proteins fusions (page 13, lines 5-11). This is equivalent to an expression environment containing one or more heterologous nucleic acids encoding one or more polypeptides of a biomolecule complex, just as instantly claimed. Cleavage sites for various proteolytic enzymes can be engineered into the expression vectors so that the cleavage sites reside in multiple locations of the peptide (page 14, lines 13-16). The most preferred protease is the TEV NIA protease which cleaves at a specific consensus cleavage site (page 14, lines 29-16). This is the same specific proteolytic cleavage site for TEV protease NIA as instantly claimed. Following protease treatment the released protein can be purified in a variety of ways, including affinity chromatography (page 15, lines 17-21). Affinity chromatography is well known in the art of purification by means of using affinity for another substance immobilized on a solid support; for instance an antigen is purified by affinity chromatography on a column of specific antibody molecules covalently linked to beads. Useful affinity tags include polyhistidine tags, IgG binding domain of protein A and glutathione S-transferase (page 15, lines 24-27). Moreover, the affinity tags can be easily removed by incorporating a protease cleavage sites (pages 15-16, lines 30-2). Example 2 teaches expression of recombinant genes whereby the recombinant fusion proteins are detected (page

21, lines 5-9). Example 3 teaches purification of recombinant proteins whereby the fusion proteins containing polyhistidine residues can be further purified by passing the supernatant over a nickel-chelating resin and further eluting the proteins from an immuno-affinity column (pages 21-22, lines 26-4).

Therefore, Darzins et al., teach a method for purifying substances providing an expression environment containing heterologous nucleic acids with cleavage sites encoding at the two subunits of a biomolecules, fused to at least two different affinity tags; maintaining the expression environment to allow expression of the fusion proteins with the affinity tags and purifying the polypeptide whereby the binding of the polypeptide occurs via one affinity tag being bound to a support material.

Previously Presented Arguments

8. Applicants' argue that Darzins et al., teach the over-production of one desired protein. However, it is noted that the method of Darzins et al., achieve that same results using the same steps and same biomolecules as those instantly claimed. The MPEP section 2123 teaches that patents and publications are relevant as prior art for all they contain, and the use of these references is not limited to what the inventors describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain." *In re Heck*, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983) (quoting *In re Lemelson*, 397 F.2d 1006, 1009, 158 USPQ 275, 277 (CCPA 1968)). A reference may be relied upon for all that it

would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). See also *Celeritas Technologies Ltd. v. Rockwell International Corp.*, 150 F.3d 1354, 1361, 47 USPQ2d 1516, 1522-23 (Fed. Cir.1998) Therefore applicants' argument is not persuasive. Moreover, it is noted that the claims fail to recite any limitations on protein expression with respect to over expression. Therefore, because of the claims broad and inclusive language, a teaching of over expression is also embraced by the claims since the claims are not limited in that way. Thus Applicants'" reliance that the instant method claims do not require over expression is not persuasive, since the claims are not limited to exclude over expression.

Applicants' argue that Darzins et al., fail to teach purification of complexes. However Darzins et al., teach purification in a variety of ways, including affinity chromatography, wherein affinity chromatography is well known in the art of purification by means of using affinity for another substance immobilized on a solid support; for instance an antigen is purified by affinity chromatography on a column of specific antibody molecules covalently linked to beads (page 15, lines 17-21). Furthermore, Darzins et al., at Example 3 entitled Purification of recombinant proteins, at pages 21-22, lines 10-16, clearly teach purification steps. Thus, contrary to Applicants'" assertion, Darzins et al., teach a method of purification.

Applicants' argue that the method of Darzins et al., is exclusively suited for gram-positive bacteria and cannot provide the correct post-translational modification which are required for the biological activity of subunit/complexes. However, Applicants'" claims do not exclude the use of gram-positive vectors. Moreover, the simply require an expression environment and the gram-positive bacteria of Darzins et al., meet that limitation. Since the prior art expression environment is capable of performing the use the same claimed use, it meets the limitations of the claim. With respect to the correct post-translational modification which are required for the biological activity of subunit/complexes, the correct folding is of great importance because when the expressed polypeptide is a subunit of a protein it will bind to the other subunits of the complex only when it is in its native form (see page 7, lines 4-11, of the instant specification). However, Darzins et al., teach expressing proteins in their native form. Darzins et al., teach a method that overcomes that problem of having formed large amounts of partially folded polypeptides gram-positive bacteria. Gram-positive secretion systems provide several advantages such as being capable of exporting proteins beyond the cell wall that retain their native conformation, thereby allowing one to establish purification protocols based on the functional properties of the active protein. Thus, the rejection is maintained and Applicants'" arguments have not been found persuasive.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Darzins et al., (WO 96/40943 published December 19, 1996) in view of Zheng et al., (1997). Darzins et al., (WO 96/40943) has been discussed above, however Darzins et al., do not teach affinity tags consisting of at least one calmodulin binding peptide. The claim is further drawn to a method for purification wherein one of the affinity tags consists of at lest one calmodulin binding peptide.

Zheng et al., teach expression vectors for high level protein production, one-step purification and direct labeling of calmodulin-binding peptide (CBP) fusion proteins. CBP proteins can be used in calmodulin affinity chromatography methods (abstract). A common strategy employed to facilitate the purification of recombinant proteins is to fuse the proteins of interest to another peptide or protein, i.e., affinity tags which have specific ligand and hence can rapidly and efficiently purify the protein (page 55, para. 2). Other popular affinity tags include polyhistidine tags, protein A, and epitopes for different antibodies (pages 55-56, para. 2). The CBP tag is small and less likely to affect the biological function of the recombinant fusion protein of interest (page 56, para 1). The CBP tag can be effectively removed by cleavage with thrombin (page 56, para. 2).

Thus CBP can be expressed with recombinant fusion proteins, used in affinity chromatography assays and removed from fusion proteins.

It would have been prima facie obvious at the time of the invention was made to exchange the affinity tags used in the method for purifying biomolecules and/or protein complexes as taught by Darzins et al., for the affinity tag of Zheng et al., because Zheng et al., teach that calmodulin binding protein affinity tags can be expressed with recombinant fusion proteins, used in affinity chromatography assays and cleaved from fusion proteins. One would have a reasonable expectation of success in simply exchanging an alternative and functionally equivalent affinity tag since Zheng et al, teach that such tags are known to be useful in the art of affinity purification and that such tags function to aid in the purification process. Moreover, no more than routine skill would have been required for one skilled in the art to use CBP tags since the prior art clearly teaches purification with similar and equivalent affinity tags.

Previously Presented Arguments

10. In response to applicant's arguments against the Zheng et al., reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to

do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the use of alternative and functionally equivalent affinity tags would have been desirable to those of ordinary skill in the art based on their ability to be expressed within recombinant fusion proteins. Moreover, CBP tags are known in the art to be used in affinity chromatography assays and have the ability to be cleaved from fusion proteins. Thus, contrary to Applicants" assertion of unexpected advantages, one would have a reasonable expectation of success because one having ordinary skill in the would have been motivated to make such a change as a mere alternative or equivalent affinity tag since Zheng et al, t clearly teach the advantages of purification with CBP affinity tags. Therefore Applicants"' arguments are not found persuasive.

Conclusion

11. No claims allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached on Monday-Thursday and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864. The fax

phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ja-Na Hines
July 5, 2005